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EXAMINER
LOEB, BRONWEN

ART UNIT	PAPER NUMBER
1636	12

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/744,384	Applicant(s) STUDER ET AL.	
	Examiner Bronwen M. Loeb	Art Unit 1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

P riod for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 January 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-11,14,15 and 18-24* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *18 and 19* is/are allowed.

6)☒ Claim(s) *1-11,14,15 and 20-24* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☒ The proposed drawing correction filed on *14 January 2002* is: a)☒ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *10* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

This action is in response to the amendment filed 14 January 2002 in which claims 1, 14 and 18 were amended, claims 12, 13, 16 and 17 were cancelled and new claims 20-24 were presented.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claims 1-11, 14, 15, and 18-24 are pending.

Drawings

1. The corrected or substitute drawings were received on 14 January 2002. These drawings are acceptable to the Examiner and have been approved by the Draftsperson.

Response to Amendment

2. The rejection of claims 12, 13 and 16 under 35 U.S.C. §101 has been withdrawn in view of Applicant's amendment in which these claims were cancelled.

The rejection of claims 12 and 13 under 35 U.S.C. §112, first paragraph for lack of enablement has been withdrawn in view of Applicant's amendment canceling these claims.

The rejection of claims 1-13 under 35 U.S.C. §112, second paragraph as being indefinite has been withdrawn in view of Applicant's amendment.

The rejection of claim 17 under 35 U.S.C. §102 as being anticipated by any one of Lee et al, Johe et al or Deloulme et al has been withdrawn in view of Applicant's amendment in which this claim was cancelled.

3. Claims 14 and 15 stand rejected under 35 U.S.C. §112, first paragraph for lack of enablement for reasons of record and as further discussed below.

Claims 1-11 stand rejected under 35 U.S.C. §112, first paragraph, scope of enablement, for reasons of record and as further discussed below.

Claims 14 and 15 stand rejected under 35 U.S.C. §112, second paragraph as being indefinite for reasons of record and as further discussed below.

4. New grounds of rejection are presented below.

Response to Arguments

5. With regard to the rejection of claims 14 and 15 under 35 U.S.C. §112, first paragraph for lack of enablement, Applicant's arguments have been fully considered but are deemed not persuasive.

Applicant argues that the references cited in the enablement rejection are not relevant because the method of the invention is not simply traditional gene therapy but is "more sophisticated" in that "it combines cell replacement therapy with gene therapy, thereby overcoming many of the obstacles to traditional gene therapy." Specifically, Applicant states that the well known problem of targeting is overcome in their method and point to page 15 in the specification as support. Review of page 15 reveals no mention of targeting; page 13 appears to be what Applicant intended to point out

wherein there is a brief discussion of "Methods of Administration". While administering the reaggregates directly into the patient's brain may overcome the problem of targeting, there remains the problem of sustained gene expression. Furthermore, neural transplantation approaches face the well known obstacle of poor graft survival (see for instance p. 12 first column of Björkland (2000 Neural transplantation in neurodegenerative disease. Wiley, Chichester (Novartis Foundation Symposium) p. 7-20)). Applicant refers to a review article (Wartiovaara (2000)) summarizing talks about gene therapy approaches to neurodegenerative diseases and specifically refers to the talk by Evan Snyder. While NSC's may be transduced in vitro and express the transduced genes for long periods of time, it is unclear that results from in vitro growth and expression conditions can be reliably extrapolated to in vivo conditions. It is further unclear if transduced precursor cells which are then made to differentiate in vitro, as is claimed by Applicant, express transduced genes for long periods of time either in vitro or in vivo. Furthermore, it is clear from the overall Wartiovaara review article that gene therapy/cell transplantation is considered a promising strategy by experts in the field but certainly not a predictable or routine method of treatment.

Applicant further argues that the specification need not contain an example if the invention is otherwise disclosed in such a manner the one of skill in the art will be able to practice the invention without undue experimentation and states that the specification teaches how to prepare the dopaminergic neurons and one of skill in the art would know how to transform them. The specification does not, however, teach how to maintain the

expression of the transformed gene in in vivo conditions to provide a therapeutic effect, nor does it provide any teachings on how to maintain graft survival.

Regarding neural cell transplantion, Applicant argues that over 200 patients have been transplanted with fetal negril cells with confirmed clinical improvement and cites Olanow et al (1996). Olanow et al clearly does not characterize the work with fetal negril cells to be predictably successful. Olanow et al state that "fetal nigral transplantation is a complex procedure" (p. 103, second column) and discuss at length (pp. 103-106) some of the known variables influencing graft failure which is thought to account for the failures of the preliminary clinical data being presented. Olanow et al conclude that "the variables that optimize cell survival and clinical benefit following fetal nigral transplantation remain to be defined in the hope of obtaining more pronounced and consistent clinical benefit" (p. 107). Furthermore, Applicant's invention is drawn to transformed, in vitro differentiated neuron cells not fetal negril cells. There is no evidence by Olanow et al, Applicant or any other prior art, that any clinical results with fetal negril cells can be predicatably extrapolated to dopaminergic cells which have been transformed and generated by in vitro proliferation and differentiation of CNS precursor cells.

Applicant also points out that they've demonstrated therapeutic effect and long term survival and function integration in Example 5. This example uses a rodent made to have neurological dysfunction by a chemical lesion. While Applicant states the rat model used in their example is art recognized and cites two articles. Both articles indicate that there are well-characterized rodent models of Parkinson's disease.

Applicant's claims however are not drawn to a method for treatment of Parkinson's disease and the full scope of the claimed invention must be enabled. There is no evidence that this rat model has any predictive value in Huntington's disease, Alzheimers or any other CNS disorder such as stroke or epilepsy. Furthermore, it is certainly not unequivocally accepted by experts in the field of neural transplantation that results in rodents and mice are predictive for success in humans. For instance, Olanow et al state that "the lack of graft rejection in rodents and primates does not guarantee similar results in humans" (p. 106). Wartiovaara states that "it is difficult if not impossible to compare the pathological behavior of mice to that of man, even if the cellular and biochemical changes are similar" (p. 6-7). See also p. 360 of Svendsen et al ((1999) TINS 22:357-0364) wherein it is stated "it is not certain that human cells...will show equivalent properties to mouse ES cells". Indeed, the stem cell transplantation has been characterized as "fraught with obstacles" despite all of advances using mouse and rodent stem cells. See Bohler et al (1999 Cells Tissues Organs 165:237-245). Therefore, the rejection is maintained.

6. With regard to the rejection of claims 1-11 under 35 U.S.C. §112, first paragraph, scope of enablement, Applicant's arguments have been fully considered but are deemed not persuasive.

Applicant argues that the representative example enables the genus as a whole and that the specification provides ample guidance in disclosing that precursor cells should be obtained during "a sensitive period" and specifies such a period for rats and humans and asserts that the conserved nature of neural stem cells is recognized in the

art. This is not persuasive for several reasons. First, the art does not unequivocally accept that neural stem cells have a conserved nature across species. For instance, as discussed above, many experts in the art do not believe that results using mouse or rodent neural stem cells are predictive for human stem cells. (See for instance Wartiovaara (2000), Svendsen et al (1999) and Olanow et al (1996)). Secondly, the specification does not provide a definition for "a sensitive period", which is not a term of art, but rather simply provides ranges of time. There is no disclosure teaching why that particular time period for rats and for humans is sensitive that would enable one to predict what time period would be "sensitive" for any other organism having a central nervous system. There is no definition in terms of biochemical or molecular features which would provide guidance for other species to obtain the appropriate precursor cell for proliferation and differentiation in vitro. Thus, the claims are only enabled for CNS precursor cells obtained from rats or humans; the full scope of the claim is not enabled. The rejection is maintained.

7. With regard to the rejection of claims 14 and 15 under 35 U.S.C. §112, second paragraph as being indefinite, Applicant's arguments have been fully considered but are deemed not persuasive.

Applicant argues that the amendments to claim 14 overcome the rejection that the method lacks a step that clearly relates back to the preamble. The amended method steps result in differentiated transformed neuronal cells being administered to a patient, however, the preamble states "a method of introducing a gene product into a

brain of a patient". There are no method steps directed to getting the gene product into the brain of the patient.

New Grounds of Rejection

Claim Rejections - 35 U.S.C. § 112

9. Claims 20-23 are rejected under 35 U.S.C. §112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The following factors have been considered in formulating this rejection (*In re Wands*, 858F.2d 731, 8 USPQ2d 1400 (Fed. Cir. 1988): the breadth of the claims, the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability or unpredictability of the art, the amount of direction of guidance presented, the presence or absence of working examples of the invention and the quantity of experimentation necessary.

The present claims are very broad. Claim 20 is drawn to a method of treating a patient for any neurological disorder comprising administering in vitro proliferated and differentiated dopaminergic neuron cells.

The nature of the invention is a method of treatment by neural cell transplantion.

An analysis of the prior art as of the effective filing date of the present application shows that neural cell transplantion has shown very few documented successes and is an undeveloped and unpredictable field. As noted by several experts in the field, a key

obstacle to success in neural cell transplantation is graft survival. See for instance p. 2435 of Clarkson et al (1999) and Olanow et al (1996) pp. 103-107. While there are many factors thought to be important to graft survival, successful optimization remains to be achieved (p. 107 of Olanow et al). A clear understanding of the etiology of each neurodegenerative disease is necessary for neural transplantation success but such information is not known for all neurodegenerative diseases. See p. 537 of Björkland et al (2000 Nature Neuroscience; cited by Applicant). Yet even with knowledge of the etiology, the results of neural cell transplantation are unpredictable. Fetal nigral transplantion in Parkinson's disease patients yielded a range of results from no effect to mild-to-moderate improvement in motor features yet yielded more dramatic benefit in chemically-induced parkinsonism. It is unknown why the chemically-induced parkinsonism benefits more than Parkinson's disease. Furthermore, as discussed above, the art does not unequivocally agree that mice or rodent data are predictive for humans.

The relative skill of those in the art of neural transplantion is high.

The area of the invention is unpredictable because, as discussed above, it is unknown if results in rats or mice can be extrapolated to other species, particularly humans, all of the variables involved in graft survival have not be defined, nor have they been optimized, and one cannot predict that transplantation would be beneficial even in those diseases for which there is a great deal of knowledge about the etiology.

The present specification provides little direction or guidance to support the claimed invention. The claim encompasses any neurological disorder; the specification

discusses only three specific diseases (Parkinson's Disease, Alzheimer's Disease, Huntington's disease).

The working example disclosed uses a rat model of Parkinson's disease in which the rat brain is chemically lesioned. There are no working examples for any other neurodegenerative disease, nor is there any data demonstrating the in vitro proliferated and differentiated dopaminergic neurons will have any therapeutic effect in any other species than rat.

The quantity of experimentation necessary to carry out the claimed invention Is high as the skilled artisan could not rely on the prior art or the instant specification to teach how to use the claimed method. In order to determine how to use the claimed method to treat any neurodegenerative disorder, one would have to determine that the disease mechanism involves loss of functioning dopaminergic neurons, if in vitro proliferated and differentiated dopaminergic neurons could provide benefit in, for instance, a human and how to overcome the well known obstacle in neural cell transplantation of poor graft survival. Since neither the prior art nor the specification provides the answers to all of these questions, it would require a very large quantity of trial and error experimentation by the skill artisan to answer them.

Based on the broad scope of the claims, the unpredictability in the area of the invention, the lack of sufficient guidance or working examples in the specification and the quantity of experimentation necessary, it would clearly require undue experimentation by one of skill in the art to determine how to make and use the claimed

method of treating a patient for any neurological disorder comprising administering in vitro proliferated and differentiated dopaminergic neuron cells.

10. Claims 20-24 are rejected under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 20 is vague and indefinite for lacking a method step which clearly relates back to the preamble.

Claim 23 is vague and indefinite in reciting "The method according to claim 22 wherein introducing a therapeutically offensive amount" however claim 22 does not recite a step of introducing a therapeutically offensive amount, but only a step of introducing a therapeutically effective amount. Furthermore, the specification does not define "therapeutically offensive amount" nor is this a term of art.

Claim 24 is vague and indefinite in reciting "an assay for a substance" without reciting a purpose for the assay. It is suggested that the preamble be amended to recite language similar to that taught on p. 15, lines 28-20 to overcome this rejection; a step clearly relating back to the preamble is also necessary.

Claim Rejections - 35 USC § 102

11. Claims 1, 3 and 7-11 are rejected under 35 U.S.C. 102(b) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Buc-Caron (Neurobiology of Disease (1995) 2:37-47). Buc-Caron teaches a method of generating dopaminergic neuron cells by proliferating and differentiating CNS precursor cells. The CNS

precursor cells were obtained from human fetus brains, either in toto (and therefore comprising nucleus raphe cells) or separated into anterior and posterior (including mesencephalon) fractions, when the fetuses were aged between 5 and 12 weeks of gestation. Proliferation was in the presence of bFGF. Differentiation occurred in serum-containing medium, resulting in a heterogenous mixture of cells comprising mostly neuroepithelial and/or neuroblastic cells; it is assumed that this heterogenous culture comprises cholinergic neuronal cells and serotonergic cells. Absent evidence to the contrary, it is assumed that the serum-containing medium, OptiMEM, a proprietary medium, with 15% heat-inactivated fetal bovine serum, comprises ascorbic acid. Alternatively, it would have been obvious to one of ordinary skill at the time of the invention to supplement the growth medium taught by Buc-Caron with ascorbic acid. One of ordinary skill in the art would have been motivated to do so because ascorbic acid is an essential micronutrient and is known to play a role in stimulating presursor cells to differentiate. See for instance Eldridge et al (J. Cell Biol. (1987) 105:1023-1034) which teaches the role of ascorbic acid in in vitro differentiation of axon-related Schwann cells.

Claim Rejections - 35 USC § 103

12. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

13. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

14. Claims 1-4 and 7-11 are rejected under 35 U.S.C. 103(a) as being unpatentable over Buc Caron, in view of Studer (Current Protocols in Neuroscience (1997) Vol. 1, Unit 3.3, pp. 3.3.1-3.3.12; cited in IDS Paper #6). Buc Caron is applied as above. Buc Caron does not teach incubating the precursor cells in a roller tube or the use of 50 to 500 x 10^3 cell/ml of precursor cells in the proliferation step. Studer teaches three different methods of cultivating and differentiating rat embryonic nigral cells from the mesencephalon, including the use of roller tubes for the proliferation step and 500 x 10^3 cell/ml of precursor cells in the proliferation step. See entire article. At the time the invention was filed, it would have been obvious to one of ordinary skill in the art to use the cultivation methods taught by Studer in the method taught by Buc Caron. One of ordinary skill in the art would have been motivated to do so as the Studer reference is published in the "gold standard" of neuroscience techniques, Current Protocols in Neuroscience, and because the growth in roller tubes is advantageous for the study of complex developmental events and for transplantation studies in rats.

Conclusion

Claims 18 and 19 are allowed. Claims 1-11, 14, 15 and 20-24 are rejected.

Claims 5, 6, 14, 15 and 20-24 are free of prior art.

Certain papers related to this application may be submitted to Art Unit 1636 by facsimile transmission. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 C.F.R. § 1.6(d)). The official fax telephone numbers for the Group are (703) 308-4242 and (703) 305-3014. NOTE: If Applicant does submit a paper by fax, the original signed copy should be retained by applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers in the Office.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Bronwen M. Loeb whose telephone number is (703) 605-1197. The examiner can normally be reached on Monday through Friday, from 10:00 AM to 6:30 PM. A phone message left at this number will be responded to as soon as possible (usually no later than the next business day after receipt by the examiner).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Remy Yucel, can be reached on (703) 305-1998.

Any inquiry of a general nature or relating to the status of this application should be directed to Tracey Johnson, Patent Analyst whose telephone number is (703) 305-2982.

Bronwen M. Loeb, Ph.D.
Patent Examiner
Art Unit 1636

March 24, 2002

REMY YUCEL, PH.D
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